DOCKET NO. SPC89-05*

Exhibit C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on 2-10-93

Hamilton, Brook, Smith & Reynolds, P.C.

G. J. Hamilton 2/10/93

Signature Date

DECLARATION

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Gunnar Aberg, declare:

THAT I am a citizen of Sweden and a resident of the Town of Westborough, Worcester County, Massachusetts;

THAT I am Vice-President of Research and Development, Pharmaceutical Division, Sepracor, Inc., Marlborough, Massachusetts. From 1968 to 1973 I was Director of Pharmacology at Bofors-Nobel Pharma, from 1974 to 1978 I was Group Leader in General Pharmacology at AB Haessle, from 1978 to 1980, I was Director of Pharmacology at Astra Pharmaceuticals, from 1980 to 1982 I was Director of

Cardiovascular Pharmacology at Ciba-Geigy; and from 1982 to 1988 I was Director of Pharmacology, and from 1988 to 1992 Executive Director of Pharmacology, at Bristol-Myers Squibb;

That I am a graduate of the University of Linkoping, Sweden from which I hold a Ph.D. in Pharmacology and of the University of Goteborg, Sweden from which I hold a Ph.D. in Zoophysiology, and that I am an Associate Professor in Applied Pharmacology at the University of Linkoping, Sweden;

That I have twenty-eight years' industrial experience in the area of pharmacology research;

That I am an author of 86 articles on pharmacology, including eight articles on adrenergic β-blockers and β-agonists and that I am an inventor on seven U.S. patents and 6 pending U.S. applications and that I have made numerous presentations before professional societies on the subject of adrenergic drugs;

That I have reviewed carefully the Office Action dated August 10, 1992 in the above case. I have also reviewed the application in the above case and the art cited by the examiner in his rejection, namely Chemical Abstracts 89:121259m (1978), Brittain et al., Harley et al., Hawkins, et al. and Buckner et al.; and as a result of my review and general knowledge of the subject area, I make the following analysis:

The Chemical Abstracts reference teaches that racemic albuterol may be used to treat asthma, but there is no teaching in the reference that would motivate one skilled in the art to go to the considerable trouble and expense of isolating and administering either enantiomer.

Brittain et al. show that both enantiomers and the racemic mixture of albuterol are very selective for β_2 receptors, but the isomeric activity ratio of R and S albuterol on isolated tracheal muscle (β_2) vs atrial muscle (β_1) is "impossible to calculate...because the isomers are virtually inactive on this tissue." R(-) and racemic albuterol inhibited acetylcholine-induced bronchospasm in

anesthetized guinea pigs at dose-levels of 2.5 to 100 µg/kg. The corresponding figure for S(+) albuterol was 50 to 5000 µg/kg, indicating, as expected, a lower potency of the S-isomer. No difference was reported between the effects of R(-) and R,S albuterol in the anesthetized guinea pig. The potency ratio of R(-) vs racemic albuterol could be calculated when the compounds were tested in a model of acetylcholine-enhanced pulmonary resistance in the dog, and indicated that the R(-)-isomer was approximately twice as potent as the racemate. On the isolated guinea pig trachea, Brittain et al. found R-albuterol to be approximately equipotent with the racemate (table 1; page 146). Thus, from a study of the Brittain et al. reference I have not been able to conclude anything definitive regarding either (1) the selectivity of the R isomer vs the racemate, or (2) the relative potencies of the two compounds.

Hartley and Middlemiss teach that both isomers and the racemic mixture of albuterol act on β_2 receptors rather than β_1 receptors. The effects of the R isomer and the racemic mixture are equiactive on β_2 receptors of the intact guinea pig trachea; indeed, it can be calculated from the reported data that the racemate is 1.5 times as potent as the R(-) isomer. There is no clear teaching with regard to selectivity between β_1 and β_2 for the two isomers and the racemate, because the ratio of trachea vs left atrium activity is roughly the same for the R isomer and for the racemate, and the ratio of trachea to right atrium shows a better ratio for the R isomer but partial agonist activity for the R isomer and not for the racemate. Thus, no conclusion can be drawn from Hartley and Middlemiss as to whether the R isoner would enjoy any advantage over racemic albuterol in terms of side effects.

Hawkins and Klease characterize the study of Hartley and Middlemiss by stating that Hartley reported that racemic albuterol was 1.5 times as active as the minus enantiomer. In their studies, Hawkins and Klease found that the R enantiomer was approximately twice as potent as the racemate. They did

not examine any tissue other than guinea pig trachea so that no conclusion relating to relative selectivity could be drawn. Thus if one ignored the teachings of Brittain et al. and particularly of Hartley et al., one could interpret the Hawkins publication to disclose a small potency advantage for the R isomer. On a theoretical basis if the S isomer were totally inactive, the racemate (being a 50-50 mixture) should have a theoretical potency of about 50% that of the R isomer; Hawkins' results would be consistent with that hypothesis.

The study by Buckner and Abel examines the ratio of activity of the R and S isomers of albuterol in guinea pig atria and guinea pig trachea. They concluded "even though the potencies of single isomers may differ as much as twenty-four fold between atria and trachea, the stereoselectivity for production of activity is the same." That is, the selectivity, as measured by the ratio of tracheal to atrial activity, is the same for the two isomers. Buckner did not examine racemic albuterol so no conclusion can be drawn as regards any potency advantage of a single pure R isomer vs the racemate.

The combined teachings of all of the foregoing references provide little clear direction. If one ignores Hartley and one of Brittain's experiments, with the intention of selectively extracting from the references any advantage associated with the R isomer, it appears that the R isomer may enjoy a theoretical two-fold potency advantage over the racemate. However, as a practical matter, even were this the case, it would not motivate a person of scientific skill and experience in the pharmaceutical industry to prepare and administer the pure R isomer instead of the racemate. This is because a process for the resolution of racemic albuterol would inevitably produce R albuterol in less than 50% yield, whereas the use of the racemic albuterol would, at worst, provide 50% of the potency of the pure R. Thus there is little to be gained by resolving the racemate.

As regards the question of diminution of side effects of

R-albuterol vs racemic albuterol, there is no clear teaching in any of the references that R-albuterol would enjoy an advantage over racemic albuterol on the basis of its selectivity between β_1 and β_2 receptors.

In the instant application, Barberich and Young disclose an unexpected diminution in side effects when the pure R isomer of albuterol is administered. Side effects of drugs that have a predominant β_2 agonist component can arise from four presently recognized and well characterized receptor interactions: (a) non-adrenergic effects; (b) interaction of the β-agonist with α-receptors; (c) interaction of the β_2 agonist with β_1 receptors; and (d) interaction of the β_2 agonist with β_2 receptors. The interactions of these drugs with β_3 receptors (the adipocyte β-receptors) have not been well defined and are therefore not discussed in this declaration. Non-adrenergic effects can be triggered by interaction with any of the hundreds of other receptors and by non-receptor interactions, and they can originate from portions of the drug molecule outside the β_2 pharmacophore. They are, for this reason, difficult to predict or screen for. Interaction of β-agonists with α-receptors are known in epinephrine but are not of clinical significance in agonists like albuterol. Interaction of β_2 agonists with β_1-receptors, causing pulmonary agents to exhibit cardiac side effects, is well documented for isoproterenol and has been discussed above for albuterol. The literature cited in the office action provides no evidence for an advantage of either enantiomer of albuterol on the basis of β_2 vs β_1 specificity.

Interaction of β_2-agonists at β_2-receptors can give rise to tachyphylaxis and perhaps to sensitization in addition to the desired bronchodilation. While well documented, these effects are only recently beginning to be understood. Tachyphylaxis appears to arise from mechanisms that are subsequent to the receptor-ligand interaction. [See Strasser et al. Adv. Exp. Med. Biol. 231, 503-517 (1988)]

The recent publications of Morley et al. [Brit. J. Pharmacol. 104, Supp. 295P (1991)] and Chapman et al. [Trends in Pharmacological Science 12 231-232 (1992)], which I have also reviewed, provide newly available support for applicants' disclosure in this respect. The Morley and Chapman references disclose that the S(+) isomer in bronchial tissue causes a hypersensitivity to allergen. This hypersensitivity is not usually observed in acute administration because the bronchodilator effect of the R enantiomer masks the hypersensitivity. However, on subchronic treatment with racemic albuterol Morley et al. were able to detect the hypersensitivity. They concluded from their experiments that the desired bronchodilator effect was prone to tachyphylaxis while the undesirable hypersensitivity is less prone to tachyphylaxis. Indeed, in the Chapman et al. paper the authors recommend that it may be prudent to remove enantiomers that were previously thought to be biologically inert. Their results support a previously undisclosed advantage to the use of pure R enantiomer in that the side effect of paradoxical hypersensitivity is likely to be ameliorated.

I further declare that all statements of the foregoing declaration made of my own knowledge are true and that those made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Signed by me this 8th day of February, 1993.

Gunnar Aberg

...ton & Hanburys—Cont.

...clinically relevant laboratory abnormalities related to Ventolin Inhalation Solution, administration were determined in these studies.

In comparing the adverse reactions reported for patients treated with Ventolin Inhalation Solution with those of patients treated with isoproterenol during clinical trials of 3 months, the following moderate to severe reactions, as judged by the investigators, were reported. This table does not include mild reactions.

Percent Incidence of Moderate to Severe Adverse Reactions

Reaction	Albuterol n=65	Isoproterenol n=65
Central nervous system		
Tremor	10.7%	13.8%
Headache	3.1%	1.5%
Insomnia	3.1%	1.5%
Cardiovascular		
Hypertension	3.1%	3.1%
Arrhythmias*	0%	3.0%
Palpitation*	0%	22.0%
Respiratory		
Bronchospasm†	15.4%	12.0%
Cough	3.1%	5.0%
Bronchitis	1.5%	5.0%
Wheezing	1.5%	1.5%
Sputum increase	1.5%	1.5%
Dyspnea	1.5%	1.5%
Gastrointestinal		
Nausea	3.1%	0%
Dyspepsia	1.5%	0%
Systemic		
Malaise	1.5%	0%

*The finding of no arrhythmias and no palpitations after albuterol administration in this clinical study should not be interpreted as indicating that these adverse effects cannot occur after the administration of inhaled albuterol.

†In most cases of bronchospasm, this term was generally used to describe exacerbations in the underlying pulmonary disease.

Ventolin Rotacaps® (albuterol sulfate) for Inhalation: Results of clinical trials with Ventolin Rotacaps for Inhalation, 200 mcg, in 172 patients aged 12 years and older (adults) and 129 patients aged 4-12 years (children) showed the following side effects:

Central Nervous System: Adults: Headache, 4 of 172 patients (2%); nervousness, 2 of 172 (1%); dizziness, insomnia, lightheadedness, each in <1%. *Children:* Headache, 6 of 129 (5%), dizziness and hyperactivity, each in <1%.

Gastrointestinal: Adults: Burning in stomach in <1%. *Children:* Nausea and/or vomiting in 5 of 129 (4%), stomachache in 2 of 129 (2%), diarrhea in <1%.

Oropharyngeal: Adults: Throat irritation in 3 of 172 (2%); dry mouth and voice changes, each in <1%. *Children:* Throat irritation in 3 of 129 (2%), unusual taste in 2 of 129 (2%).

Respiratory: Adults: Cough in 3 of 172 (2%), bronchospasm in 2 of 172 (1%). *Children:* Cough and nasal congestion, each in 3 of 129 (2%), bronchospasm and epistaxis, each in 2 of 129 (2%).

Miscellaneous: Adults: Tremor in 2 of 172 (1%). *Children:* None reported.

Ventolin® (albuterol sulfate) Syrup: The most frequent adverse reactions to Ventolin Syrup in adults and older children were tremor, 10 of 100 patients, and nervousness and dizziness, each in 9 of 100 patients. Other reported adverse reactions were headache, 4 of 100 patients; dizziness and increased appetite, each in 3 of 100 patients; hyperactivity and excitement, each in 2 of 100 patients; and hallucinations, sputum, and sleeplessness, each in 1 of 100 patients. The following adverse effects each occurred in fewer than 1 of 100 patients: muscle spasm, disturbed sleep, epigastric pain, cough, palpitations, stomachache, irritable behavior, dilated pupils, sweating, chest pain, and weakness.

In young children 2-6 years of age, some adverse reactions were noted more frequently than in adults and older children. Excitement was noted in approximately 30% of patients and nervousness in 15%. Hyperkinesia occurred in 4% of patients, with insomnia, bronchospasm, and gastrointestinal symptoms in 2%, each. Anorexia, emotional lability, pallor, fatigue, and conjunctivitis were seen in 1%.

Ventolin® (albuterol sulfate) Tablets: The most frequent adverse reactions to Ventolin Tablets were nervousness and tremor, with each occurring in approximately 20 of 100 patients. Other reported reactions were headache, 7 of 100 patients; tachycardia and palpitations, 5 of 100 patients; muscle cramps, 3 of 100 patients; and insomnia, nausea, weakness, and dizziness, each in 2 of 100 patients. Drowsiness, flushing, restlessness, irritability, chest discomfort, and difficulty in micturition each occurred in fewer than 1 of 100 patients.

The reactions to Ventolin Syrup and Ventolin Tablets are generally transient in nature, and it is usually not necessary to discontinue treatment. In selected cases, however, dosage may be reduced temporarily; after the reaction has subsided, dosage should be increased in small increments to the optimal dosage.

OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Hypokalemia may also occur.

Treatment consists of discontinuation of albuterol together with appropriate symptomatic therapy.

As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of aerosol albuterol.

The oral LD_{50} in male and female rats and mice was greater than 2000 mg/kg. The inhalational LD_{50} could not be determined.

Dialysis is not appropriate treatment for overdosage of Ventolin® (albuterol) Inhalation Aerosol, Ventolin Rotacaps® (albuterol sulfate) for Inhalation, or Ventolin® (albuterol sulfate) Syrup. The judicious use of a cardioselective beta-receptor blocker, such as isoproterenol hydrochloride, is suggested, bearing in mind the danger of inducing an asthmatic attack. There is insufficient evidence to determine if dialysis is beneficial for overdosage of Ventolin® (albuterol sulfate) Inhalation Solution, Ventolin® Nebules™ (albuterol sulfate) Inhalation Solution, or Ventolin® (albuterol sulfate) Tablets.

DOSAGE AND ADMINISTRATION

Ventolin® (albuterol) Inhalation Aerosol: For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 4 years and older is two inhalations repeated every 4-6 hours; in some patients, one inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations are not recommended.

The use of Ventolin Inhalation Aerosol can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the inhaler. Safe usage for periods extending over several years has been documented.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma that would require reassessment of therapy.

Exercise-Induced Bronchospasm: Prevention: The usual dosage for adults and children 12 years and older is two inhalations 15 minutes before exercise.

For treatment, see above.

Ventolin® (albuterol sulfate) Inhalation Solution: The usual dosage for adults and children 12 years of age and older is 2.5 mg of albuterol administered three to four times daily by nebulization. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, dilute 0.5 mL of the 0.5% inhalation solution with 2.5 mL of sterile normal saline solution. The flow rate is regulated to suit the particular nebulizer so that Ventolin Inhalation Solution will be delivered over approximately 5-15 minutes.

The use of Ventolin Inhalation Solution can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the inhalation solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma that would require reassessment of therapy.

Ventolin® Nebules™ (albuterol sulfate) Inhalation Solution: The usual dosage for adults and children 12 years and older is 2.5 mg of albuterol administered three to four times daily by nebulization. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, administer the contents of one sterile unit dose Nebule® (3 mL of 0.083% inhalation solution) by nebulization. The flow rate is regulated to suit the particular nebulizer so that Ventolin Nebules Inhalation Solution will be delivered over approximately 5-15 minutes.

The use of Ventolin Nebules Inhalation Solution can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the inhalation solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma that would require reassessment of therapy.

Ventolin Rotacaps® (albuterol sulfate) for Inhalation: The usual dosage for adults and children 4 years of age and older is the contents of one 200-mcg capsule inhaled every 4-6 hours using a Rotahaler® inhalation device. In some patients, the contents of two 200-mcg capsules inhaled every 4-6 hours may be required. Larger doses or more frequent administration are not recommended.

The use of Ventolin Rotacaps for Inhalation can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the Ventolin Rotacaps for Inhalation formulation.

If a previously effective dosage regimen fails to provide adequate relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma that may require reassessment of therapy.

Exercise-Induced Bronchospasm: Prevention: The usual dosage of Ventolin Rotacaps for Inhalation for adults and children 12 years of age and older is the contents of one 200-mcg capsule inhaled using a Rotahaler 15 minutes before exercise.

Ventolin® (albuterol sulfate) Syrup: The following dosages of Ventolin Syrup are expressed in terms of albuterol.

Usual Dosage: The usual starting dosage for adults and children over age 14 is 2 mg (1 teaspoonful) or 4 mg (2 teaspoonfuls) three or four times a day.

The usual starting dosage for children 6-14 years of age is 2 mg (1 teaspoonful) three or four times a day.

For children 2-6 years of age, dosing should be initiated at 0.1 mg/kg of body weight three times a day. This starting dosage should not exceed 2 mg (1 teaspoonful) three times a day.

Dosage Adjustment: For adults and children over age 14, dosage above 4 mg four times a day should be used only when the patient fails to respond. If a favorable response does not occur, the dosage may be cautiously increased stepwise, but not to exceed 8 mg four times a day.

For children 6-14 years of age who fail to respond to the initial starting dosage of 2 mg four times a day, the dosage may be cautiously increased stepwise, but not to exceed 24 mg per day (given in divided doses).

For children 2-6 years of age who do not respond satisfactorily to the initial dosage, the dosage may be increased stepwise to 0.2 mg/kg of body weight three times a day, but not to exceed a maximum of 4 mg (2 teaspoonfuls) given three times a day.

Elderly Patients and Those Sensitive to Beta-adrenergic Stimulators: The initial dosage should be restricted to two or four times a day and individually adjusted to minimize adverse effects.

Ventolin® (albuterol sulfate) Tablets: The following dosages of Ventolin Tablets are expressed in terms of albuterol.

Usual Dosage: The usual starting dosage for adults and children 12 years of age and older is 2 or 4 mg three or four times a day.

The usual starting dosage for children 6-12 years of age is 2 mg three or four times a day.

Dosage Adjustment: For adults and children 12 years of age and older, a dosage above 4 mg four times a day should be used only when the patient fails to respond. If a favorable response does not occur with the 4-mg initial dosage, it should be cautiously increased stepwise up to a maximum dosage of 8 mg four times a day as tolerated.

For children 6-12 years of age who fail to respond to the initial starting dosage of 2 mg four times a day, the dosage may be cautiously increased stepwise, but not to exceed 24 mg per day (given in divided doses).

Elderly Patients and Those Sensitive to Beta-adrenergic Stimulators: An initial dosage of 2 mg three or four times a day is recommended for elderly patients and for those with a history of unusual sensitivity to beta-adrenergic stimulators. If adequate bronchodilatation is not obtained, dosage may be increased gradually to as much as 8 mg three or four times a day.

The total daily dose should not exceed 32 mg in adults and children 12 years of age and older.

HOW SUPPLIED

Ventolin® (albuterol) Inhalation Aerosol: is supplied in 17-g canisters containing 200 metered inhalations per canister. Each actuation delivers 90 mcg of albuterol from the mouthpiece. Each canister is supplied with an inhaler adapter and patient's instructions (NDC 0173-0321-88). Also available: Ventolin Inhalation Aerosol Refill 17-g canister, with patient's instructions (NDC 0173-0321-56). Store between 15° and 30°C (59° and 86°F). As with inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold. Shake well before using.

Ventolin® (albuterol sulfate) Inhalation Solution: is supplied in bottles of 20 mL (NDC 0173-0385-00) with accompanying calibrated dropper in boxes of one. Store between 2° and 25°C (36° and 77°F).

Ventolin® Nebules™ (albuterol sulfate) Inhalation Solution, 0.083%: is supplied in sterile unit dose nebules, 3 mL each, in boxes of 25 (NDC 0173-0419-00). Protect [illegible]

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Henley
#10

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner: Henley III,

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on July 19, 1995

Philip E. Hansen
Agent for Applicant
Registration No. 32,700

Date of Signature: July 19, 1995

To: Assistant Commissioner for Patents
Application Processing Division
Customer Correction Branch
Washington, D.C. 20231

Sir:

COMMUNICATION REQUESTING CORRECTION OF OFFICIAL FILING RECEIPT

Applicant encloses a copy of the corrected Official Filing Receipt issued in connection with the above-identified application.

The following error appears in the corrected filing date:

"12/27/94"

should read

--11/7/94--

in light of the granting of applicants' petition to be accorded the above filing date. A copy of the Decision on Petition is enclosed herewith.

Applicant hereby requests that a corrected official Filing Receipt indicating the filing date of November 7, 1994, be issued.

Respectfully submitted,

Philip S. Hansen
Agent for Applicant
Registration No. 32,700

Dated: July 19, 1995

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July 19, 1995

FILING RECEIPT

CORRECTED

UNITED STATE EPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO	DRWGS	TOT CL	IND CL
08/335,480	12/27/94	1205	$365.00	0701-027C	0	72	3

PHILIP R. HANSEN
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ALBANY, NY 12203-5160

RECEIVED
JAN 6 1995
HESLIN & ROTHENBERG, P.C.

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Applicants Processing Division's Customer Correction Branch within 10 days of receipt. Please provide a copy of the Filing Receipt with the changes noted thereon.

Applicant(s)

TIMOTHY J. BARBERICH, CONCORD, MA; JAMES W. YOUNG, STILL RIVER, MA.

CONTINUING DATA AS CLAIMED BY APPLICANT-
THIS APPLN IS A CON OF 08/163,581 12/07/93 PAT 5,362,755
WHICH IS A CON OF 07/896,725 06/09/92
WHICH IS A CON OF 07/461,262 01/05/90

FOREIGN FILING LICENSE GRANTED 01/20/95 * SMALL ENTITY *

TITLE

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

PRELIMINARY CLASS: 514

(see reverse)

DLEV011930

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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Washington, D.C. 20231

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MAY 30 1995

SPECIAL PROGRAM
EXAMINATION UNIT

In re Application of
Barberich et al.
Application No.: 08/335,480 : DECISION ON PETITION
Filed: November 7, 1994
Docket No. 0701.027C

This is a decision on the petition filed December 27, 1994, requesting that the above-identified application be treated as a continuation application under 37 CFR 1.60 and accorded a filing date of November 7, 1994.

The application, which is a continuation application under 37 CFR 1.60, was deposited on November 7, 1994. Application Division mailed a Notice on December 16, 1994, stating that a copy of the prior application specification was missing, specifically noting pages 2 and 3 as being omitted, requiring a copy of the omitted application specification pages, and stating that the filing date of the application would be the date of receipt of the missing items. However, it is noted that prior application Serial No. 08/163,581 issued as Patent No. 5,362,755 on November 8, 1994. Therefore, a filing date on or before November 8, 1994, is necessary to establish copendency between the prior application and the above-identified application in order for the above-identified application to be considered a proper filing under 37 CFR 1.60.

In response on December 27, 1994, a copy of the missing specification pages were filed. The application was erroneously assigned a filing date of December 27, 1994, and the application was forwarded to Group 1200 for examination.

On March 9, 1995, a nonfinal Office action was mailed setting a three month shortened statutory period for response.

Subsequently, the application was forwarded to this Office for review of the petition filed December 27, 1994. The petition, includes a check for the $130.00 petition fee. Petitioner argues that the failure to file a true copy of the prior application, on filing was inadvertent. Petitioner requests that the earlier filing date be accorded this application.

A review of the application file, reveals that a copy of the prior application specification pages 2 and 3 are not among the application papers filed November 7, 1994. Also, 8 total pages of specification, including the claim pages and abstract are identified on the copy of the postcard receipt accompanying the petition; whereas, 10 total pages of specification, including the claims and abstract were present in the prior application. Thus, it is concluded from the available evidence that a true copy of the prior application specification pages 2 and 3 were not submitted, on filing.

37 CFR 1.60(b) states, in part, that if a true copy of the prior application as filed is not filed with the application or if the statement that the application papers are a true copy is omitted, the application will not be given a filing date earlier than the date upon which the copy and statement are filed, unless a petition with the fee as set forth in 37 CFR 1.17(i)(1) is filed which satisfactorily explains the delay in filing these items.

In this application, the failure to file a true copy of the prior application, on filing, has been deemed to be an inadvertent error.

As construed above, the petition to accord the application a filing date of November 7, 1994, is granted.

The application is being forwarded to Application Division for correction of the records to reflect a November 7, 1994, filing date, and for further processing with the filing date of November 7, 1994, as a continuation application under 37 CFR 1.60 of prior application Serial No. 08/165,581, using the application papers filed November 7, 1994, and the copy of pages 2 and 3 of the prior application specification filed December 27, 1994.

Thereafter, the application will be returned to Examining Group 1200 to await response to the March 9, 1995, office action. The three month shortened statutory period for response continues to run from the March 9, 1995, date of mailing of that office action.

for

Fred A. Silverberg
Senior Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

PK

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/335,480	11/07/94	BARBERICH	0701.027C

EXAMINER	
HENLEY III, R	
ART UNIT	PAPER NUMBER
1205	11

12M2/0925

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5 COLUMBIA CIRCLE
ALBANY NY 12203-5160

DATE MAILED: 09/25/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 6/12/95 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-4, 6 and 8 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-4, 6 and 8 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTO-326 (Rev. 2-95)

CLAIMS 1-4, 6 AND 8 ARE PRESENTED FOR EXAMINATION

Applicants' amendment and attachments thereto, including the declaration of Dean Allan Handley, filed June 12, 1995 have been received and entered into the application. Accordingly, the specification at page 1 and claims 1 and 6 have been amended and claims 5, 7 and 9-12 have been cancelled. In view thereof, the obviousness-type double patenting rejection set forth in the last Office action dated March 9, 1995 at page 5 is withdrawn.

NEW GROUD OF REJECTION

Claim 8 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim depends from cancelled claim 7.

Claims 1-4, 6 and 8 remain rejected under 35 U.S.C. § 103 as being unpatentable over Muttari et al. in view of Brittain et al., Hawkins et al. and Hartley et al., each of record, for the reasons of record as set forth in the last Office action at pages 2-4 as applied to claims 1-12.

Applicants' arguments and the Handley declaration have been carefully considered, but fail to persuade the Examiner of error in his determination of obviousness.

In attempting to refute the instant prima facie presumption of obviousness, applicants have argued at pages 5 and 6 of their amendment that the skilled artisan would not have found the presently claimed subject matter to be obvious because the cost of separation of the stereoisomers exceeds the potential advantage of a possible increase in activity for the R(-) enantiomer. The Examiner believes, however, that regardless of the cost, the skilled artisan would have found it obvious that the R(-) enantiomer of albuterol could be successfully employed for the claimed purpose. While economic considerations are important, they are not necessarily determinative in deciding whether or not to develop and market a particular eutomer or racemate. This appears clear from the fact that in the Testa et al. article provided by applicants, nowhere in their decision tree is there consideration given to cost. Indeed, at page 129, column 1, under the heading "Asking the Right Questions", the authors state that "[t]he decision whether to develop and market the eutomer or the racemate of a given chiral drug should belong to scientists only and be based primarily on scientific evidence". Here, it is believed that the pharmacological characteristics of R(-) albuterol would have imbued the skilled artisan with at least a reasonable expectation that it could be

effectively employed for the treatment of acute asthma. Thus, the Examiner's position is maintained.

Respecting the Handley declaration, it cannot be afforded the significance urged. The declarant at page 6 states that "[t]he S enantiomer and racemic albuterol induced sustained tremors in animals; R-albuterol may be somewhat less tremorigenic, but it is not clear whether the difference is significant"(emphasis added). Given such an expression of doubt by the declarant as to the significance of the reported test results, it is not seen that the declaration permits the Examiner to reach a reasoned conclusion that R albuterol possesses an unexpectedly superior side effect profile in the treatment of acute asthma as compared to the racemate or the S isomer.

Accordingly, the claims are deemed to remain properly rejected.

None of the claims are allowed.

Applicants' amendment necessitated the new grounds of rejection. Accordingly, THIS ACTION IS MADE FINAL. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO

37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Henley whose telephone number is (703) 308-4652.

RAYMOND HENLEY, III
PRIMARY EXAMINER
GROUP 1200

Henley: rjh
September 22, 1995

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/334,480	11/7/94	Barbericht	0701.027C

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EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Philip Hansen* (3) Doug Reedick

(2) John McCullough (4) Ray Henley (PTO)

Date of Interview 16 November 1995

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative)*

Exhibit shown or demonstration conducted: ☐ Yes ☐ No. If yes, brief description: declaration to be filed showing E isomers differ activity on [Ca^{2+}] alone + w/ CARbachol Challenge

Agreement ☐ was reached with respect to some or all of the claims in question. ☒ was not reached.

Claims discussed: all - generally

Identification of prior art discussed: all - generally

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Reviewed prior art, agreed that differences were present between the isomers but could not agree that differences were unexpected. Applicants are invited to submit a response outlining what was known would have been expected vs. what applicants have found + how findings support a conclusion of ~~obviousness~~ non-obviousness in light of Evans Adamson

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

Examiner's Signature

PTO-413 (REV. 2-93) ORIGINAL TO BE INSERTION IN RIGHT HAND FLAP OF FILE WRAPPER

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